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Adopting the Therapeutic Orphan: An Examination of FDA and Congress' Efforts to Promote the Inclusion

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Adopting the Therapeutic Orphan: An Examination of FDA and Congress' Efforts to Promote the Inclusion of Children in Clinical Drug Studies

INTRODUCTION

Physicians regularly prescribe drugs to children, by necessity, without the guidance of clinical trials that test drugs to determine their safety and efficacy in this population. Often times, such therapies have harmful effects, creating grave dangers and risks, including death, for some pediatric patients. Physicians' extensive off-label use of drugs to treat children may lead one to conclude that children are already being used as research subjects everyday. Yet, prior to the passage of the FDA's Final Rule mandating drug sponsors to test drugs on children and the pediatric exclusivity provision of the Food and Drug Modernization Act, there was little incentive for the pharmaceutical industry to include children in their clinical studies and, thus, they did not. However, as a result of both initiatives, the number of children in clinical trials has

risen. There is an estimated 45,000 children participating in industry-sponsored testing of new drugs, up from about 16,000 in 1997.

This paper examines both the Food and Drug Administration's Final Rule, which mandates drug sponsors to conduct pediatric research on their products prior to FDA approval and Section 111 of the Food and Drug Modernization Act, which provides economic incentives for drug sponsors to include children in research studies on their products. This paper concludes that Congress should renew the pediatric exclusivity provision of the Food and Drug Modernization Act, but with modifications as to provide incentives to drug sponsors for testing products on children that are not as burdensome to the elderly and the poor. After a historical review of the ills of pediatric testing, the paper discusses the need for more studies to be conducted regarding the effects of drugs commonly prescribed in children. The paper then discusses the need for regulation in clinical trials involving children. Next, the paper discusses past efforts of Congress and the FDA to encourage drug sponsors to include the pediatric population in research trials before marketing their products and then examines the latest efforts of both to encourage such studies. In the final section, the paper proposes modifications to FDAMA Section 111 to ensure that the legislation is meeting its goal of including children in more clinical trials in efforts to provide more labeling information in therapies used on children.

I.

THE NEED FOR REGULATION IN PEDIATRIC RESEARCH

The history of experimental research on human beings is plagued with horrific instances of abuse such as World War II Nazi experiments on people that resulted in the Nuremberg trials¹, the Tuskegee experiments

¹Leonard H. Glantz, Conducting Research with Children: Legal and Ethical Issues, J. Amer. Acad. of Child and Adol. Psych., 34: 1283-91, at 1285 (1996).

in which African-American men were denied treatment for syphilis², and the Willowbrook experiments in which institutionalized children were intentionally infected with hepatitis and observed to determine the effects of a vaccine for the disease.³ Recent examples, such as the death of a three-year-old in a cancer study treatment⁴ and the death of a nine-month-old given an experimental drug for reflux,⁵ serve as reminders that using humans as research subjects continue to pose significant risks. As such, modern scientists have approached the continued use of humans as research subjects with caution, especially where children are involved.

A. Historical Abuses of Children in Clinical Trials

Children were historically excluded from clinical studies, with the exception of vaccine development. There was hesitation concern on the part of many over drug therapy in the pediatric population. Indeed, the dogma of the day was simple: it was considered unethical to enroll children in experiments.⁶ Children were a population to be protected from the unpredictability of therapeutic trials.⁷

Nonetheless, numerous clinical studies conducted in the development of vaccines continued to have large pediatric populations.⁸ During the nineteenth century, the amount of pediatric research conducted increased

²See *id.* at 1285.

³Robert M. Nelson, *Children as Research Subjects*, in *Beyond Consent: Seeking Justice in Research* 47, 49 (Jeffrey P. Kahn, et al., eds., 1998). In this study, researchers exposed a group of mentally challenged students to a strain of the hepatitis virus intentionally, so that they could “understand the natural history and prevention of this disease.” This experiment is discussed in greater detail *infra* at Section II. A.

⁴Alice Dembner, Dangerous Dosage to Make Pediatric Medicine Safer, *Boston Globe*, February 18, 2001, at A1. A 3-year-old diagnosed with a cancerous stomach mass and researchers in cancer study misdiagnosed the child’s condition and he later died. An investigation by the *Boston Globe* revealed, “Medical experiments across the country appear to have killed at least eight children and subjected hundreds more to harmful side effects in the last seven years.” *Id.* at A1.

⁵Drug Study Blamed in Baby’s Death: 9-Month Old was Part of Heartburn Medical Trial, *Milwaukee Journal Sentinel*, April 28, 2000, at A9.

⁶Jane E. Henney, Remarks at the Institute of Medicine National Academy of Sciences Roundtable on Research and Development of Drugs, Biologics, and Medical Devices, entitled, “Rational Therapeutics for Infants and Children” (May 24, 1999). (transcript available at <http://www.verity.fda.gov/search97cgi/>) (visited May 1, 2001).

⁷See *id.*

⁸Leonard H. Glantz, Research with Children, 24 *J.L. & Med.* 213, 215 (1994) (stating that “children have been particularly subjected to abuses by researchers and ‘those who do research with children today have

substantially in an earnest effort to improve children's health through advanced vaccinations and inoculations.⁹ Although the researchers conducting these trials made significant oncological contributions by curing serious childhood diseases, they often placed pediatric research subjects at considerable risk.¹⁰

High-risk experiments involving medical research on children continued throughout the late nineteenth century. Researchers primarily focused their experiments upon institutionalized children in asylums and orphanages¹¹ as control groups for research on measles and other diseases¹², theories, and medical treatments.¹³ The inherent dangers in these trials were manifested through many cases.¹⁴ For instance, in a North Carolina orphanage in 1912, children were administered an experimental tuberculosis vaccine¹⁵ and were later found to have a greater tendency to contract the disease than the children who had not received the experimental treatment.¹⁶

Newer, more sophisticated drugs and medical tools, such as the x-ray, prompted continued medical research on children in the twentieth century, with a particular interest in metabolism and digestion.¹⁷ Many of these experiments required pediatric subjects to undergo medically unnecessary procedures and discomfort.¹⁸ The

inherited the legacy of researchers who have come before them.''). Accredit all paragraphs regarding the history of experimentation on children to his book.

⁹Susan E. Lederer & Michael A. Grodin, Historical Overview: Pediatric Experimentation, in Children as Research Subjects, 3, 19 (Michael A. Grodin & Leonard H. Glantz, eds., 1994) (stating that the history of pediatric research is filled with stories of abuses).

¹⁰See id. at 4-8 (describing pediatric trials that led to smallpox vaccinations and how pediatric research led to anti-toxins for diphtheria, which was main cause of death in 19th century children.)

¹¹Weisstub, et al., Biomedical Experimentation with Children: Balancing the Need for Protective Measures with the Need to Research on Human Subjects 380, 381 (David N. Weisstub, ed., 1998) (quoting a New York pediatrician who said that asylum children were ideal subjects for research because of the researcher's ability to control subjects.)

¹²See id. at 380-81 (noting that trials were conducted for measles similar to those of smallpox trials).

¹³Glantz, supra note 8, at 216 (describing experiments with x-rays and other experiments where doctors performed spinal taps on children to determine if they are harmful.)

¹⁴See Lederer & Grodin, supra 9, at 7 (explaining that medical interest in diseases like cancer, leprosy, syphilis, gonorrhea, tuberculosis and yellow fever prompted researchers to infect children and other research subjects deliberately).

¹⁵See id. at 8 (describing 1912 tuberculosis study where 262 children at a North Carolina orphanage were injected with an experimental tuberculosis vaccine).

¹⁶See id. at 8 (noting that when North Carolina Public Health Services tested subjects in 1914, "guinea pigs who had received the vaccine yielded more quickly to tubercular infection than those not vaccinated").

¹⁷See id. at 9 (explaining doctors' use of x-rays to study normal development of children, and the great interest in studying human digestion using stomach tubes in children and infants).

¹⁸See id. at 10 (describing gastrointestinal studies that caused subjects to become extremely ill and other tests where children had to be sedated and restrained to comply with protocol requirements.)

negative publicity surrounding these trials, however, led to increased scrutiny of these abusive experiments by members of the medical community and society-at-large.¹⁹

Pediatric subjects continued to endure mistreatment well into the second half of the twentieth century despite this increased scrutiny.²⁰ The hepatitis testing conducted at the Willowbrook State School beginning in 1955 and continuing through the early 1970s is one of the most infamous examples of pediatric clinical testing abuse.²¹ Although researchers conducting this clinical trial obtained parental permission, the parents were not fully apprised of the risks involved in the experiment.²² The head of the research team defended the Willowbrook experiment, explaining that research subjects were not placed at an increased risk of serious illness than the school's other students. In fact, he predicted that research subjects were at a lower risk of serious illness than the school's other students due to the poor conditions that existed at the school.²³ Despite the head researcher's defenses of the study, critics continued to question its merits²⁴ While this study and others similar to it shed light on the ills of pediatric research, abuses continue in this country and throughout the world even today.

In the early 1990s in New York City, thirty-six healthy children between the ages of six and ten years old

¹⁹See Glantz, *supra* note 8, at 216 (describing 1941 incident where editor of *Journal of Experimental Medicine* refused to publish study in which 12 healthy infants were inoculated with herpes, even though these children were volunteered by parents for study).

²⁰See Lederer & Grodin, *supra* note 9, at 11-13 (explaining that groups opposing animal research began to oppose pediatric research subject abuse in late 19th century, and were later joined by members of medical community and journalists).

²¹A.E. Ryan, *Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical* 23 *Fordham International Law Journal*. 848 (2000) (quoting Robert M. Nelson, *Children as Research Subjects*, in *Beyond Consent: Seeking Justice in Research* 47, 49 (Jeffrey P. Kahn, et al., eds., 1998). In this study, discussed briefly *supra*, a group of mentally challenged students were exposed to a strain of the hepatitis virus intentionally, so that researchers could "understand the natural history and prevention of this disease.")

²²See *id.* at 51. (noting "' ' consent forms that parents signed to allow their children to be infected with the virus' read as though their children were to receive a safe vaccine'").

²³See *id.* at 50 (citing interviews with the head of Willowbrook research team, Saul Krugman, in which he states that because subjects were protected from common diseases at Willowbrook, participation in the hepatitis study was more safe than the school's ordinary living conditions, thus, an ethical study.)

²⁴See *id.* at 50 (explaining that critics of the study questioned whether parents were forced into consenting by promises of better conditions for the children, why similar tests were not conducted on adult staff members of the facility, and why other prevention measures were not taken to control the spread of disease.)

participated in a research study where they were given doses of the diet drug fenfluramine. Prior to this study, the FDA had removed this drug from the market for causing death in adult patients, however, exposure to fenfluramine was found by researchers to measure a hormone in the subjects' brains that was supposedly linked to antisocial behavior. In the course of this three-year study, researchers forced children to fast for eighteen-hour periods and then drew multiple blood samples from catheters inserted in their veins. The result of this process left some of the children feeling nauseous and complaining of headaches. While these horrific examples illustrate the extreme need for regulation in the area of medical testing of human beings, especially children²⁵, the importance of safe clinical studies cannot be overstated. Regulation in this area helps to achieve the necessary balance between conducting safe research trials and the need for the valuable information about the effects of drugs in children which is derived from such experiments.

B. Pharmaceutical Companies' Exclusion of Children from Clinical Studies

Many pharmaceutical companies resist conducting research on children²⁶ because of the ethical and legal concerns involved in conducting pediatric trials, and the difficulty recruiting subjects²⁷ for testing. A study on the effects of the drug Enbrel on children with rheumatoid arthritis demonstrates the difficulties pharmaceutical companies face when conducting pediatric research.²⁸ First, the market for pediatric medicines is small. Of the estimated two million Americans with rheumatoid arthritis, less than 100,000 are children, and only half of those children would be eligible.²⁹ Thus, drug companies can expect little in return for

²⁵Presently, there is an estimated 45,000 children participating in industry-sponsored testing of new drugs, up from about 16,000 in 1997. These numbers are expected to continue to rise with the promulgation of initiatives to encourage safe pediatric testing. See Dembner, *supra* note 4, at A1, quoting Christopher-Paul Milne, a senior research fellow at the Tufts University Center for the Study of Drug Development.

²⁶Ryan, *supra* note 21.

²⁷Ralph E. Kauffman, Scientific Issues in Biomedical Research with Children, in Children as Research Subjects, 30, 38 (Michael A. Grodin and Leonard H. Glantz, eds. 1994) (stating that many protocols are impeded because researchers are not able to enroll sufficient number of subjects that conform to study's criteria.)

²⁸Dembner, *supra* note 4.

²⁹See *id.*

conducting such costly studies³⁰ on children without some external financial incentive. In the case of the Enbrel study, researchers tested adults and children simultaneously to get the drug approved as an “orphan drug,” a lucrative designation given to treatments for rare diseases.³¹ Orphan drug status entitles a drug company to tax credits and seven years of “market exclusivity,” whereby generic companies are precluded from competing with the name brand drug until the exclusive license expires.³²

Not only is the demand of drugs for pediatric patients relatively small, few therapeutic indications are unique to the pediatric patient population.³³ Furthermore, from an actuarial perspective, humans spend about 60 to 80 years as adults, whereas they spend only approximately 16 years as children.³⁴ Finally, since off-label prescribing is considered perfectly acceptable medical practice, physicians are still able to administer drugs to children without costly clinical trials.³⁵ As a result, there are few incentives for pharmaceutical companies to develop drugs and drug dosing guidelines for infants and children. Thus, a large number of medications commonly prescribed for children are not tested on pediatric subjects, creating a grave dangers and risks for young patients.³⁶

II.

THE NEED FOR INFORMATION ABOUT THE EFFECTS OF DRUG THERAPIES IN CHILDREN

³⁰R. Coopman, The Pros and Cons of the Policy on Pediatric Trials, Chain Drug Review, 23: RX 8 (2000) (stating that the average testing and approval process for a drug is estimated to cost anywhere from \$200,000 to \$3 million).

³¹Dembner, *supra* note 4.

³²Orphan Act, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended at 21 U.S.C. § 360aa-360ee (1994); 26 U.S.C. § 45C (1994); 42 U.S.C. § 236 (1994)).

³³Jeffrey L. Blumer, Off-Label Uses of Drugs in Children, American Academy of Pediatrics, 104: 598-602, 598 (1999).

³⁴*Id.* at 598.

³⁵Veronica Henry, Off-Label Prescribing: Legal Implications, J. Legal Med. 20:3 (September, 1999) at 1 (stating that the American Medical Association estimates 40%-60% of all prescriptions in the United States are written for drugs being used for something other than their approved purpose.)

³⁶See National Institutes of Health (‘‘NIH’’), NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, March 6, 1998 (stating that AAP has reported that ‘‘only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials for use in pediatric patients’’).

A.

Physiological Differences Between Adults and Children

Because children are subject to many of the same diseases as adults, physicians often treat children, by necessity, with the same drugs and biological products used by adults, even if these products have not been tested on children.³⁷ Physicians' extensive off-label³⁸ use of drugs to treat children has leads one to the conclusion that children are already being used as research subjects everyday. Because physicians prescribe drugs to children without the controlled supervision of a clinical trial, such prescriptions often result in disastrous consequences for the children and their families.³⁹

The physiological differences between children and adults require scientists to conduct pediatric research.⁴⁰ The most distinguishing feature differentiating children from adults are the significant physical and maturation changes that occur.⁴¹ The course of an individual's development with regard to drug absorption, metabolism, and excretion substantially restricts the extrapolation of data from adults to children.⁴² One horrific example of children metabolizing drugs differently than adults was the wide-spread use of the antibiotic chloramphenicol in premature infants to treat infections. A study in 1959 revealed that babies were unable to metabolize the drug properly. Chloramphenicol, which had only been approved for use in adults for infections resistant to penicillin, resulted in "gray baby syndrome" and death for some infants who accumulated toxic levels of the drug in their system.⁴³ Furthermore, not only is a child's physiology significantly

³⁷J. Rosato, The Ethics of Clinical Trials: A Child's View, 28 J.L. Med. & Ethics 362 (2000) at note 28.

³⁸Blumer, *supra* note 33 at 599. Off-label means that while the FDA has approved the drug for adults, it has not approved or labeled it for children.

³⁹*Id.* at 598.

⁴⁰Jeffrey L. Blumer, Is Pediatric Labeling Really Necessary?, American Academy of Pediatrics, 104: [suppl] 593-597, 596.

⁴¹*Id.* at 596.

⁴²*Id.* at 597.

⁴³See J.S. Abramson and M.E. Holland, Off Label Use of Antimicrobial Agents in Infants, Children and Adolescents: A time for A

different from that of an adult, but a child's physiology is different from that of another child in a different age group.⁴⁴

As a result, the differences between adults and children, and even the differences among children themselves, significantly impact whether and how a drug can be used on a pediatric patient.⁴⁵ Drug studies conducted on adults or on children of only one age group may not adequately predict whether a drug will be toxic if prescribed to a child of another age group.⁴⁶ Thus, pharmaceutical companies' failure to test medicines in children of all age groups may result in serious illness or even death.

B. Off-Label Prescriptions

Without adequate pediatric testing, physicians confront a serious ethical dilemma: prescribe medication or perform a procedure that potentially benefit the child, or refrain from this treatment due to inadequate information about its effects on children.⁴⁷ By prescribing the drug or performing the procedure, the physician may run the risk of creating an unexpected adverse effect on the child that could subject the physician to liability.⁴⁸ Conversely, by failing to prescribe the drug off-label, the doctor may be preventing the child from receiving the most effective intervention available.⁴⁹

The FDA has implemented some initiatives to improve both the quality and quantity of pediatric prescribing

Ped. Infec. Dis. J. 17: 739-44, at 742 (1998).

⁴⁴See generally Blumer *supra* note 40.

⁴⁵Kauffman, *supra* note 27 at 39 (stating that "capacity to metabolize and excrete drugs changes throughout infancy, childhood and adolescence").

⁴⁶Blumer, *supra* note 40 at 595 (explaining that adult tests may not accurately predict the minimal effective dose, maximum titrated dose, therapeutic effect or adverse reactions in the child).

⁴⁷See American Academy of Pediatrics, Committee on Drugs, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics, Feb. 1995, 286, 286 (explaining that using non-validated drugs, which fails to create data for future use, may create greater risk than administering drugs in controlled clinical trial.)

⁴⁸S. Stolberg, Once Excluded, Children Now Take Part in Drug Tests, Milwaukee Journal Sentinel (February 11, 2001) at 17A (quoting doctor who cautiously bases chemotherapy doses on height and weight, "I might be able to treat their cancer more aggressively, but I don't know how to safely do that.")

⁴⁹See *id.* at 17A. See generally Rosato, *supra* note 37v.

guidelines available to health care professionals. First, the Pediatric Studies Page for a New Drug Application was modified.⁵⁰ Prior to the modification, the manufacturer had to justify the necessity of conducting a pediatric study. Under the modification, the manufacturer must justify why a pediatric study is not going to be conducted.⁵¹

Secondly, standards were developed for clinicians to follow for the extrapolation of data from adult clinical trials, when appropriate, or for the use of selective pediatric data (pharmacokinetics) in formulating pediatric use guidelines to help physicians prescribe drugs off-label more safely.⁵² For example, one method to make the adjustment from an adult dosage to a child dosage is an extrapolation based on weight.⁵³ The arbitrariness of this method, and its failure to take into account any specific differences in drug absorption between children and adults makes this an inadequate method for determining proper dosages for children without placing them at a substantial risk for injury or even death.⁵⁴ Moreover, adjusting doses solely based on weight often underdose infants and children, while overdosing neonates.⁵⁵

Another suggested method for determining dosages of medication for children is to extrapolate dosage information from available medical literature.⁵⁶ In this instance, the clinician's decision for treatment is based on studies published in medical journals. Yet, this method is equally inadequate. Research shows that the reporting of clinical research in medical literature is burdened with paucities, including ill-prepared study designs, inaccurate documentation, questionable data collection methods, flawed statistical analyses, and indefensible conclusions.⁵⁷ Moreover, unlike the FDA's review of data from a clinical trial, journal editors and

⁵⁰See Taylor & Francis, Off Label Prescribing, J. Legal Med. 20:3 (September, 1999).

⁵¹Id.

⁵²See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling, 59 Fed. Reg. 64, 240 (1994) (amendment responding to the inadequacy of drug labels in supplying information for use in pediatric populations.) This amendment is discussed, *infra*, in Section IV.

⁵³Blumer *supra* note 33 at 600.

⁵⁴Id. at 600.

⁵⁵Id.

⁵⁶Henry *supra* note 35 at FN 110.

⁵⁷S.J. Pocock, M.D. Hughes, et al., Statistical Problems in the Reporting of Clinical Trials: A Survey of Three Medical Journals, N. Engl. J. Med. 317: 426-32, (1987) cited in Blumer *supra* note 40.

reviewers usually do not have access to all the data when reviewing the results of a clinical trial.⁵⁸ Therefore, drug therapy decisions that rely solely upon medical literature may also lead to ineffective therapy or toxic results.

Unfortunately, this practice of off-label prescribing using weight charts and medical literature by physicians often constitutes the standard of care for many children.⁵⁹ Startling statistics show that only one-fifth of all drugs on the market have been labeled for use by infants and children.⁶⁰ Moreover, 60 to 70 percent of drugs have no indication for their use in children under age 12, and 95 percent of drugs used in neonatology are administered off-label.⁶¹ As a result, children remain “therapeutic orphans,” a term coined to describe children who are experimented on outside formal clinical trials.⁶² The problem of therapeutic orphaning hinders the development and application of potentially life-saving therapies for pediatric patients, sometimes causing children to suffer grave and dangerous harm. More than 70% of all Physicians’ Desk Reference (PDR) entries have either no existing dosing information for pediatric patients or explicit statements that the safety and efficacy in children have not been determined.⁶³ This quandary is particularly evident in medications used to treat serious illnesses, such as cancer and AIDS.⁶⁴ Additionally, certain age groups are commonly excluded from drug trials, resulting in incomplete and unreliable outcomes concerning the safety

⁵⁸Id.

⁵⁹Only one-fifth of all drugs on the market have been labeled for use by infants and children. 62 Fed. Reg. 43,899-916, at 43,902, col. 1 (1997). Moreover, 60 to 70 percent of drugs have no indication for their use in children under age 12, and 95 percent of drugs used in neonatology are administered off-label. V. DeBenedette, Suffer the Children, Drug Topics, 142: 2 (January, 1998). See also Blumer supra note 33 at 599 (stating, “The prescribing of drugs for off-label use is entirely proper”).

⁶⁰62 Fed. Reg. 43,899-916, at 43,902, col. 1 (1997).

⁶¹DeBenedette supra note 59 at 2.

⁶²See Ryan supra note at 856.

⁶³Id.

⁶⁴Ryan supra note 21 at 857. (noting that less than half of FDA approved drugs used to treat human immunodeficiency virus (“HIV”) and opportunistic infections caused by HIV are labeled for use in children.) According to the AAP, 81% of the drugs listed in the 1991 Physician’s Desk Reference disclaimed all use in children, or at least disclaimed use in children of certain age groups. Id. In 1992, 79% of the 19 new molecular entities that were approved by the FDA were not labeled for use in pediatric patients. Committee on Drugs, supra note 47 at 286. In 1996, only 37% of new molecular entities with potential usefulness in children had some pediatric labeling. NIH, supra note 36 at 43902.

and effectiveness of drugs for these patients.⁶⁵ Therefore, despite the controversies surrounding medical studies that are conducted on children the scientific need for such experimentation is apparent.⁶⁶

IV.

CONGRESS' AND FDA'S PAST ATTEMPTS TO IMPROVE DRUG LABELING FOR CHILDREN⁶⁷

Prior to initiatives to encourage drug sponsors to include the pediatric population in clinical studies on drug therapies, children were likely to remain therapeutic orphans. During the past two decades, however, the medical community has expressed increased concern that the majority of drugs widely used on children lack testing regarding the safety and effectiveness of such usage. In response to this concern, Congress and the Food and Drug Administration have undertaken numerous initiatives to address the problem of inadequate pediatric testing and unsubstantial pediatric use information available in drug and biological product labeling.

The first earnest efforts to improve pediatric labeling of drugs began in 1974.⁶⁸ At that time, the FDA and the American Academy of Pediatrics (AAP) agreed to develop and implement a solution for the lack of drugs in the market labeled for pediatric use.⁶⁹ The AAP's Committee on Drugs then issued general guidelines outlining procedures for the evaluation of drugs to be used in pediatric patients. Subsequently, the FDA

⁶⁵See NIH, *supra* note 36 (explaining that there is almost no information for most classes of drugs for use in children under age two).

⁶⁶See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43900, 43901 (1997) (stating that pediatric testing is necessary to determine appropriate drug dosing guidelines, as incorrect dosing can lead to "unexpected adverse reactions," and ineffective treatment).

⁶⁸General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children, Committee on Drugs, American Academy of Pediatrics (Evanston, Ill., 1974), cited in K.R. Karst, Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry, 49 Am. U.L. Rev. 739 (2000) at FN 37.

⁶⁹See *id.*

adopted AAP's guidelines and incorporated them into clinical guidelines in 1977.⁷⁰ A couple of years later, in 1979, the FDA announced a "Pediatric Use" regulation. This regulation stipulated requirements to which drug sponsors had to comply in order to include pediatric uses on product labels.⁷¹ The regulation's requirements included a mandate that drug sponsors include information collected from clinical studies performed during a product's safety and effectiveness evaluation on the product's labeling.⁷² The 1979 regulation was amended in 1994,⁷³ thereby requiring drug sponsors to modify drug labels. Modification of a drug label was to be done based on an assessment of current pediatric data to seek either a labeling change for pediatric use or to include a statement, such as: "Safety and effectiveness in pediatric patients have not been established."⁷⁴ The amended regulation essentially gave the pharmaceutical industry the option as to whether it would conduct pediatric research and include the data on labels, or include a statement on the product indicating that such studies had not been conducted.

By failing to mandate the pharmaceutical industry to include pediatric data on labels in both the 1979 "Pediatric Use" regulations and in the amended 1994 rule, the FDA essentially removed any incentive for

⁷⁰See U.S. Department of HEW, PHS, FDA, Pub. No. 77-3041, *General Considerations for the Clinical Evaluation of Drugs in Infants and Children* (1977) (outlining the guidelines for the evaluation of drugs in pregnant women, infants and children.) cited in K.R. Karst, *supra* at 68.

⁷¹Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37, 434 (1979) (codified at 21 C.F.R. pts. 201 and 202) (saying that the final rule's purpose was to establish labeling standards for all prescription drugs.)

⁷²See *id.* at 37, 459.

⁷³Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. 64,240 (1994) (amendment responding to the inadequacy of drug labels in supplying information for use in pediatric populations.) (codified at 21 C.F.R. 201.57(f)(9)(vi) (1994)).

⁷⁴See *id.* at 64, 241. This regulation required the label to include "any limitations on the pediatric indication, need for specific monitoring, specific hazards of the drugs, differences between pediatric and adult responses to the drug, and other information related to the safe and effective use of the drug in pediatric patients." *Id.* If substantial evidence failed to support a specific pediatric indication or a pediatric use statement for a particular subgroup, the regulation required the labeling to include a statement characterizing the limitation, such as "safety and effectiveness in pediatric patients [below the age of ___] have not been established."

drug sponsors to conduct clinical studies.⁷⁵ While the purpose of the 1994 amendment to the regulation was to counteract such a result,⁷⁶ it neglected to provide an incentive to generate the inclusion of substantive pediatric information on product labels.⁷⁷ When the FDA compared the number of new molecular entities approved in 1991 with those of 1996 with the potential usefulness in pediatric patients, fifty-six percent of the products approved in 1991 had some pediatric labeling at the time of approval.⁷⁸ Yet, by 1996, this number had plummeted and only thirty-seven percent of the products approved had some pediatric labeling.⁷⁹ Further, of the seven new molecular entities approved in 1991 for which post-approval pediatric studies were promised, only one attained pediatric labeling by 1997.⁸⁰ Evidently, the pharmaceutical industry chose not to study its products for use in pediatric patients. While there was not an incentive to conduct such research, neither was there a disincentive for choosing not to conduct such a study.⁸¹

Both the Clinton Administration, through the FDA, and Congress took action to remedy this problem of excluding children from drug therapy trials.⁸² The FDA made clinical testing as well as the subsequent

⁷⁵Dianne Murphy, Statement at the Anti-Infective Drugs Advisory Comm. Meeting of the Pediatric Subcomm. (1999) (discussing the FDA's efforts in the 1970s and the agency's 1994 effort to include pediatric information on drug labels did not result in sufficient pediatric information because the Industry was given an option as to whether it will conduct the studies.)

⁷⁶See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling, 59 Fed. Reg. at 64, 241 ('The final rule revises the current 'Pediatric Use' subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more complete information about the use of a drug in the pediatric population...')

⁷⁷Althea Gregory, Denying Protection to Those Most in Need: The FDA's Unconstitutional Treatment of Children, 8 Alb. L.J. Sci. & Tech. 121, 131 (1997) (arguing that the 'Pediatric Use' regulations did not result in any changes to pediatric testing as evidenced by the fact that at least 71% of drugs still lack adequate pediatric dosing information).

⁷⁸Henney *supra* note 6.

⁷⁹See *id.*

⁸⁰See *Id.*

⁸¹See Off-Label Drug Use and FDA Review of Supplemental Drug Use and FDA Review of Supplemental Drug Applications: Hearings Before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. On Gov't Reform and Oversight, 104th Cong. 109 (1996) (statement of Ralph Kauffman, M.D., Professor of Pediatrics and Pharmacology at the University of Missouri, Kansas City and Director of Medical Research at the Children's Mercy Hospital in Kansas City, on behalf of the AAP) (stating that only approximately 20% of all drugs marketed in the United States have been labeled for use by infants and children and that since 1962, 80% or more of approved drugs have been labeled for adult use with a disclaimer that they are not approved for use by children) cited in K.R. Karst, *supra* note 68.

⁸²See FDA Acts to Make Drugs Safer for Children (released November 27, 1998) <http://www.fda.gov/bbs/topics/NEWS/NEW00666.html> (announcing the Administration's final rule to mandate pediatric studies.)

labeling of drugs mandatory for pediatric patients under the Pediatric Final Rule.⁸³ Conversely, instead of setting forth a mandate to conduct studies, Congress created incentives for drug sponsors to conduct such pediatric trials⁸⁴, resulting in FDAMA Section III.

V.

FDA FINAL RULE ON PEDIATRIC LABELING

Past attempts to protect pediatric health and provide safe and effective products for children are the hallmarks of change and innovation to the Food Drug and Cosmetics Act (“FDCA”). Strides in clinical pharmacology have identified how an array of factors affects the safety and efficacy of drugs in various host patients. Both the FDA’s Rule on Pediatric Labeling (“Final Rule”)⁸⁵ and Section 111 of the Food and Modernization Act (“Modernization Act” or “pediatric exclusivity provision”)⁸⁶ represent a culmination of the most recent efforts to include children in clinical drug trials and, thus, adopt the “therapeutic orphan.”

FDA regulations, with regard to the specific content and format of prescription drug labeling, stipulate that pediatric labeling must be based on adequate, well-controlled studies involving children.⁸⁷ Because the FDA’s customary rule has required labeling that specifies that such studies have not been conducted in children⁸⁸, many heavily used drugs in pediatric populations gained recognition of their utility and risks

⁸³See *infra* discussion on the development and implications of the Final Rule.

⁸⁴See *infra* discussion the development of the Food, Drug and Modernization Act, Section 111.

⁸⁵See Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66, 632 (1998).

⁸⁶See FDCA 505A; 21 U.S.C. 355a (providing market exclusivity for sponsors who conduct pediatric studies of drugs).

⁸⁷Policy Statement -- Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration: Subject Review, 98 PED. 143 (July 1996).

⁸⁸See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of ‘‘Pediatric Use’’ Subsection in the Labeling, 59 Fed. Reg. at 64, 241.

through clinical trial and error. Perhaps the failure of the 1994 voluntary labeling rule to increase the number of products on the market with pediatric labeling contributed to the FDA's proposal of a regulation requiring drug sponsors to conduct pediatric studies and to include the results of those studies on product labels in efforts to guarantee the safety and effectiveness of drugs for pediatric patients.⁸⁹ The FDA introduced the proposed rule on August 15, 1997. The promulgation of the Final Rule occurred on December 2, 1998 and took effect on April 1, 1999.

Although the drug manufacturers thought that the pediatric exclusivity provision of FDAMA, discussed *infra*, would provide enough incentive to develop drugs for children, the FDA did not agree. Apparently, the FDA thought that the provisions of the Modernization Act, which is presently scheduled to sunset in 2002, would be well complemented by a set of regulations requiring that all new drugs potentially helpful to children be tested in the pediatric population, with penalties for drug manufacturers who fail to comply.⁹⁰ The ultimate goal of the Final Rule is to have more drugs labeled for children, which is not a requirement for the benefits offered in the Modernization Act.⁹¹

The Final Rule distinguishes new drugs from currently marketed drugs. Under the Final Rule, the FDA presumes that sponsors will study all new drugs in pediatric patients unless a waiver of this requirement is justified.⁹² The FDA concluded that sponsors with currently-marketed products must conduct pediatric studies if: (1) the use of the product among pediatric patients is great and the absence of labeling would pose significant risks to those patients, and (2) the product's claimed indications would "represent a meaningful

⁸⁹63 Fed. Reg. at 66, 633.

⁹⁰See generally 63 Fed. Reg. 66, 632.

⁹¹See *id.*

⁹²The FDA may grant a waiver if the waiver request demonstrates that the product meets both of the following conditions: (1) The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments, and (2) the product is not likely to be used in a substantial number of pediatric patients. 63 Fed. Reg. at 66, 635, col. 2.

therapeutic benefit over existing treatments if studied in pediatric patients.” If the FDA determines that either a new or currently marketed drug provides a “meaningful therapeutic benefit”⁹³ for pediatric patients, then the sponsor must develop and test a pediatric formulation. Drug sponsors can waive this requirement when reasonable attempts to develop a pediatric formulation have failed.⁹⁴

The regulation’s final notice provides that where children are not tested without securing the appropriate waivers, penalties must be imposed,⁹⁵ the effectiveness of the regulation’s penalties for non-compliance is questionable. According to the FDA’s commentary, penalties include issuing injunctions, making findings of contempt, issuing fines, and requiring the manufacturer to assess the product’s safety and effectiveness.⁹⁶ Nevertheless, even if the regulation is violated, the drug will not be kept off or taken off the market “except possibly in rare circumstances” that are not designated.⁹⁷ Without the availability of these remedies, it is not clear whether manufacturers would choose to withstand the imposition of existing penalties rather than develop drugs for children. In addition to the other requirements of the rule, the regulations also provide that children should be tested before the new drug is approved for adults, unless a deferral is warranted.⁹⁸ It must be noted that the FDA’s legal authority to mandate pediatric studies has been questioned on grounds that the Final Rule expands the FDA’s regulatory authority beyond the powers granted to it by Congress.⁹⁹ The FDA relies on section 701(a) of the FDCA, which authorizes the FDA to issue

⁹³The term “meaningful benefit therapeutic benefit” is defined as a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population.” See 63Fed. Reg. at 66, 636.

⁹⁴See generally 63 Fed. Reg. 66,632.

⁹⁵See id.

⁹⁶63 Fed. Reg. at 66, 636, col. 2.

⁹⁷See id. at 66, 636, col.2.

⁹⁸See id.

⁹⁹Congress granted the FDA authority to set forth regulations to aid in the efficient enforcement of the FDCA. See FDCA 701(a), 21 U.S.C. 371(a) (1994 & Supp. 1997). The limits to this authority are, as with any agency, that the actions must reasonably relate to the agency’s purposes. See United States v. Nova Scotia Food Prod. Corp., 568 F.2d 240, 246 (2d Cir. 1977) (holding that a regulation

regulations for the “efficient enforcement of the [FDCA],” to buttress its argument for mandated pediatric studies.¹⁰⁰ However, drug manufacturers have argued that even the most expansive interpretation of the FDA’s cited statutory authority to mandate pediatric studies cannot encompass the FDA’s propositions for new or currently marketed drugs.¹⁰¹ If this authority is left unchallenged, it is anticipated that the FDA will expand its authority further if the Modernization Act expires on January, 2002 without renewal of the pediatric exclusivity provision.¹⁰²

VI.

FDAMA SECTION 111: THE 1997 PEDIATRIC EXCLUSIVITY PROVISION

issued under section 701(a) of the FDCA will be sustained as long as it is reasonably related to the purposes of the FDCA), cited in K. Karst, *supra* note 68.

¹⁰⁰See Final Rule, *supra* note 85 at 66, 657 (noting that section 701(a) grants the FDA authority to mandate pediatric studies for drug manufacturers).

¹⁰¹See generally letter from Bonnie J. Goldmann, M.D., Vice President Regulatory Affairs, Merck & Co., Inc., to FDA Dockets Management Branch, Docket No. 97N-0165 at 3 (Nov. 12, 1997) (arguing that the FDCA does not authorize the FDA to require pediatric studies for new or currently-marketed drugs), cited in K.R. Karst *supra* note 68.

¹⁰²See *id.*

In November 1997, Congress passed a sweeping reform of Food, Drug and Cosmetics Act with its enactment of the Federal Food and Drug Administration Modernization Act (FDAMA). This Act is considered to be the first comprehensive drug reform legislation in 35 years¹⁰³. Unlike past legislation aimed at the FDA, the FDAMA affects the majority of products under the agency's regulation: foods, drugs, and medical devices. At the time it was passed in 1997, the FDA predicted that the enforcement of this new legislation would be "one of the most demanding challenges faced by the agency in its 92-year history."¹⁰⁴

Two provisions of the FDAMA aim for performance of more clinical trials that are inclusive of likely patients. The first provision pertains to the inclusion of women and minorities in clinical studies. Taking a cautious approach, the FDAMA only directs the FDA to consult with the National Institutes of Health and pharmaceutical industry representatives to administer guidance on the inclusion of women and minorities in clinical trials.¹⁰⁵ Beyond this, the law fails to impose any further obligations on the FDA or drug sponsors to insure the inclusion of women and minorities in clinical studies.¹⁰⁶

In the second provision, the FDAMA encompasses a more proactive approach to ensuring that the pediatric population is included in clinical trials. Prior to the passing of the FDAMA, the FDA rarely mandated that a drug be studied in children. In fact, as discussed *supra*, the vast majority of drugs approved under FDCA amendments do not have approved indications for children. Ironically, both the 1938 and 1962 amendments to the FDCA, however, were the result of therapeutic catastrophes in the use of untested drugs on children.

The first amendments to the statute were made after the death of 107 children from sulfanilamide elixir

¹⁰³The last major reform to the FDCA was the 1962 Kefauver-Harris Amendments. See Kauffman, Status of Drug Approval Processes and Regulation of Medications for Children, 7 CURR. OP. PEDS. 195 (1995).

¹⁰⁴The FDA made this statement in a message to FDA Stakeholders. See Richard A. Merrill, Modernizing the FDA: An Incremental Revolution, Health Affairs, (March, 1999 – April, 1999).

¹⁰⁵See generally FDCA, Sec. 505(b)(1).

¹⁰⁶See *id.*

that used diethylene glycol as a solvent.¹⁰⁷ Prior to marketing of the elixir, no toxicity testing had been done. Similarly, another pediatric tragedy led to the passing of the 1962 amendments. The thalidomide tragedy, where children whose mothers took thalidomide during pregnancy to prevent morning sickness and their children were born with phocomelia and other debilitating birth defects,¹⁰⁸ led to the requirement that not only did drugs have to be safe, but they also had to be effective in the population in which they are to be marketed.¹⁰⁹ As a result of these amendments to the FDCA, the safety and efficacy in one population could not be transferred to another population, such as the adult population to the pediatric population. While these changes to the FDCA were significant, the problem of medication use in children without proper testing has not been solved. In effort an effort to solve this problem, Congress included a provision in the FDAMA offering economic incentives to pharmaceutical companies to conduct testing on children in Section 111 of the Act.

The birth of the pediatric exclusivity provision occurred in 1990, when attendees of a workshop held at the Institute of Medicine (“IOM”)¹¹⁰ recommended market-based incentives as a proposal to increase pediatric studies and labeling.¹¹¹ They named the proposal the “Better Pharmaceuticals for Children Act (“BPCA”).”¹¹² Following the IOM workshop, pharmaceutical industry representatives urged Senator Nancy Kassebaum (R-Kan.) to introduce the BPCA to Congress.¹¹³ Congress passed and signed the BPCA into

¹⁰⁷See Blumer *supra* note 40 at 596.

¹⁰⁸*Id.*

¹⁰⁹*Id.*

¹¹⁰The Institute of Medicine (“IOM”) is part of the National Academy of Sciences, a private, non-governmental organization. The IOM seeks to advance and disseminate scientific knowledge to the government, the private sector, the professions, and the public in an effort to improve human health.

¹¹¹See Institute of Med., National Academy of Sciences, Drug Development and the Pediatric Population: Report of a Workshop 12 (1991). (“Marion Finkel clarified the industry perspective of the FDA guidelines promoting pediatric drug studies...Pharmaceutical industry resources will be required by the initiatives therefore, incentives, such as exclusivity or some patent term extension, would be valuable.”)

¹¹²See *id.*

¹¹³See S. 3337, 102d Cong., 2d Sess. (1992) (proposing deferred effective dates for approval of applications under drug provisions. The purpose of the BPCA was to encourage the innovator industry to conduct pediatric testing on drug products not solely intended for use in children -- e.g. drugs prescribed on an off-label basis for children -- in exchange for six months of market exclusivity.)

law as part of the FDAMA in 1997.¹¹⁴

Although the Modernization Act does not mandate the inclusion of children in clinical trials, it does provide substantial financial incentives for manufacturers to undertake such studies. The primary incentive provided in the law is extending market exclusivity by six months to any existing period of marketing exclusivity or continuing patent protection if a drug sponsor agrees to conduct clinical trials in children.¹¹⁵ The pediatric studies do not have to result in new labeling for the tested drugs, nor do the studies have to show safety and efficacy in pediatric patients.¹¹⁶ Not only is the six months of additional patent protection for the specific drug tested, but it also applies to the drug's active moiety,¹¹⁷ the part of the drug's make-up that causes its physiological or pharmacological action.¹¹⁸ In certain limited circumstances, sponsors of such studies can earn an additional six-month exclusivity period.¹¹⁹

At the time this provision was enacted, it was predicted that the economic impact of the law would be substantial. Estimates ranged up to \$4 billion of additional sales revenue for brand manufacturers for the first 26 drugs tested subsequent to the new law.¹²⁰ Merck, for instance, is estimated to have gained nearly \$300 million in sales for having tested Pepcid on infants, in accordance with FDAMA Section 111.¹²¹

¹¹⁴See FDCA 505A; 21 U.S.C. 355a (Supp. 1997) (providing market exclusivity for sponsors who conduct pediatric studies of drugs). The inclusion of the BPCA in the FDAMA was a priority issue for Congress, second only to the reauthorization of the PDUFA. See Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. 301-392 (Supp. 1997)) (intending, among other things, to improve the regulation of food, drugs, devices, and biological products).

¹¹⁵See FDCA 505A(a), (c); 21 U.S.C. 355a(a), (c) (Supp. 1997) (extending market exclusivity for certain sponsors who conduct pediatric drug studies).

¹¹⁶See Elizabeth H. Dickinson, FDA's Role in Making Exclusivity Determinations, 54 Food & Drug L.J. 195, 203 (1999) (indicating that the goal of the broad grant of exclusivity is to get a maximum amount of useful pediatric information, and make this information public).

¹¹⁷See National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 39-40 (D.D.C. 1999) (holding that the term "drug" in FDAMA Section 111 should be interpreted as active moiety). This court's interpretation of the FDAMA Section 111 in Henney substantially increased the number of drugs to which market exclusivity could be extended, thereby increasing the value of the incentive to drug manufacturers.

¹¹⁸See 21 C.F.R. 314.108(a) (1999) (defining "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause a drug to be an ester, salt..., or other noncovalent derivative..., responsible for the physiological or pharmacological action of the drug substance")

¹¹⁹See FDCA 505A(h); 21 U.S.C. 355a(h) (Supp. 1997) (providing that drug sponsors may receive an additional six-month period if they satisfy all of the other requirements of this section).

¹²⁰Coopman *supra* note 31 at RX 8.

¹²¹See *id.*

There are, however, exceptions as to which drugs qualify for market exclusivity under the Modernization Act. For example, time must still remain on the patent, or the drug must not yet be approved.¹²² Furthermore, drug sponsors can earn market exclusivity only for products listed in the “Orange Book”¹²³ which are eligible for market exclusivity or protected under either the Drug Price Competition and Patent Term Restoration Act¹²⁴ or the Orphan Drug Act.¹²⁵

The initiative to conduct pediatric studies does not lie solely with drug companies under the Modernization Act. The Act outlines a multi-step procedure by which the FDA must first determine which drugs should be studied in children.¹²⁶ Moreover, the FDA must then initiate agreements with drug manufacturers to conduct such studies. After determining that information about a drug may produce health benefits among a pediatric population,¹²⁷ the Secretary of the Department of Health and Human Services (“DHHS”) must request in writing for the drug sponsor to conduct pediatric studies.¹²⁸ The written request addresses, among other things, the type of studies to be performed, study design, appropriate age study groups, and clinically endpoints to ensure that studies eligible for pediatric exclusivity provide meaningful safety and efficacy information on the use of the drug in relevant pediatric age groups.¹²⁹ Even after receipt of a written request, the drug sponsor is not obligated in any way to conduct pediatric studies and is allowed at its discretion to

¹²²See generally FDAMA 111 (codified at FDCA 505A, 21 U.S.C. 355a (Supp. 1997)).

¹²³See Food & Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations (CCH 18th ed. 1998) (listing the different types of drug patents that exist and the drugs that are currently protected under those patent categories.)

¹²⁴See Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified in scattered sections of 15 U.S.C., 28 U.S.C., 35 U.S.C., and 42 U.S.C.) (amending the FDCA to revise procedures for new drug applications, amending Title 35 of the U.S.C., and authorizing the extension of patents for certain regulated products.) This Act is also known commonly known as the Hatch-Waxman Act.

¹²⁵See Pub. L. No. 97-414, 1-4, 96 Stat. 2049-56 (1983) (codified in scattered sections of 21 U.S.C., 26 U.S.C., and 42 U.S.C.). The FDCA identifies drugs for rare diseases or conditions. See FDCA, Pub. L. No. 75-717, 526(a) (2) (A)-(B), 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. 360bb(a) (2) (A) -- (B) (1994)) (defining “rare disease or condition” as one which affects fewer than 200,000 people in the United States for which drug sales are not reasonably expected to exceed drug development costs.

¹²⁶See FDCA 505A(b); 21 U.S.C. 355a(a) (Supp. 1997) (outlining FDA procedures to determine which drugs should be tested in children.)

¹²⁷See FDCA 505A(b); 21 U.S.C. 355a(b) (Supp. 1997) (requiring the DHHS to develop list of drugs which may produce healthy benefits in the pediatric population and, thus, qualify for exclusivity.)

¹²⁸See FDCA 505A(d); 21 U.S.C. 355a(d) (Supp. 1997) (stipulating the various procedures and protocols involved in applications for pediatric exclusivity).

¹²⁹See *id.*

conduct such studies only to reap the benefits of the market exclusivity incentive.¹³⁰ Finally, the Act directs the FDA to annually update the listing of drugs for which additional pediatric information may improve children's health.¹³¹ Since the FDAMA came into effect, the FDA has requested studies to be performed on a significant number of drugs, covering a variety health ailments prevalent in children¹³²

Because Congress passed the Modernization Act after the FDA's proposed rule mandating pediatric study (but before the rule was finalized), the necessity of both incentives has been questioned since their passing. Yet, both the Final Rule and the pediatric exclusivity provision, as efforts to increase the number of children in clinical trials that test the effects of drugs on them, are necessary when examined closely. First, the Final Rule is intended to be product-specific. As such, the Final Rule is limited only to a specific indication for a specific drug product, whereas the Modernization Act applies to the entire active moiety of a drug product. The Final Rule shifts the inquiry from whether children should be tested to when children should be tested. The pediatric exclusivity provision, on the other hand, provides an economic incentive for drug sponsors to comply with the FDA's Final Rule. In achieving the goals of both initiatives, which is to have more clinical trials that are inclusive of children conducted, the Modernization Act is still an incentive to do such, even if the FDA's authority to mandate pediatric research is challenged.¹³³ Insofar as the Modernization Act and the Final Rule may overlap, it is the FDA's responsibility to notify drug sponsors about the possibility of gaining FDAMA market exclusivity.

¹³⁰See CDER, FDA, Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act, at 4 (Sept. 1999) <http://www.fda.gov/cderguidanceindex.htm> (“Issuance of a written request to a sponsor does not require the sponsor to conduct pediatric studies described in the written request. It is the sponsor's decision whether to conduct the studies and possibly gain pediatric exclusivity”).

¹³¹See FDCA 505A; 21 U.S.C. 355a(b) (Supp. 1997) (requiring the Secretary of the DHHS to consult with experts in pediatric research to develop and publish a list of drugs that may qualify for pediatric exclusivity not later than 180 days from the enactment of the FDAMA).

¹³²The FDA has issued 137 Written Requests for pediatric studies under 505A of the Federal Food, Drug, and Cosmetic Act (visited April 20, 2001) <http://www.fda.gov/cder/pediatric/wrlist.htm>.

¹³³See discussion of the questionability of the FDA's authority to promulgate the Final Rule *supra* at Section III.

In compliance with the FDAMA's requirement for the FDA report to Congress on the effectiveness and adequacy of pediatric exclusivity provision, the FDA released a report on the status of the section ("status report"), including suggestions for modification, on January 1, 2001.¹³⁴ Although initial reports showed that the FDA was slow to grant the market exclusivity incentives promised in the Modernization Act,¹³⁵ the status report concludes that the pediatric exclusivity provision has been highly effective in achieving its goal of generating pediatric studies on many drugs and in providing useful new information in labeling drugs and biological products. More specifically, at the time the report was written, the FDA had issued more than 157 written requests asking for 332 studies. These studies would potentially involve more than 20,000 pediatric patients. Additionally, the FDA reported that it had received more than 191 proposals from sponsors to conduct pediatric studies. In fewer than three years, more than 58 pediatric studies had already been conducted. Reports from these studies had been submitted, and exclusivity granted to 25 drugs. The status report indicated that drugs that have or soon will have pediatric use information in their labeling include those drugs used to treat conditions in children such as HIV, asthma, diabetes, acid reflux disease, hypertension, juvenile rheumatoid arthritis, obsessive-compulsive disorder, and pain.

In addition to reporting on the effectiveness of provision, the status report also addresses the adequacy and the economic impact of the provision, while also making recommendations for modifications of the provision when it expires January 1, 2002. With regard to the provision's adequacy, the status report said that the current exclusivity provision is inadequate as an incentive for drug sponsors to conduct testing on older antibiotics and other drugs lacking market exclusivity or patent protection. Moreover, the incentive is not adequate to encourage research trials for certain younger age groups, especially the neonatal age group for

¹³⁴See FDCA 505A(k); 21 U.S.C. 355a(k) (Supp. 1997) (providing that the FDA shall conduct a study and report to Congress not later than January 1, 2001). See the full report at <http://www.fda.gov/cder/pediatric/reportcong01.pdf>, herein after cited as "Status Report to Congress."

¹³⁵Karst *supra* note 68 at 767.

whom an appropriate trial cannot be designed until studies of older pediatric age groups have been submitted and analyzed.

The status report also found that the provision's market exclusivity incentive is also inadequate failure to encourage studies in drugs with low sales because the value of the exclusivity does not offset the costs of the studies. As a result, a number of drugs that have been identified as important to children, but for which the incentive has little or no value, remain unstudied. For example, of the ten most frequently prescribed drugs for children that lacked adequate labeling as set forth by the FDA in 1994, six have no remaining exclusivity or patent life. As such, their sponsors were unable to take advantage of incentives under the pediatric exclusivity program. Thus, even after the passage of the Modernization Act, the six drugs remain inadequately studied and labeled for the pediatric population.

Finally, the status report showed that although a second period of exclusivity is available in the law, it, too, is inadequate because its limited scope precludes sponsors from being able to utilize this option.

While the pediatric exclusivity provision should reduce certain types of health care expenditures, it also increases others. The status report estimates that the cost of pediatric exclusivity will add less than one-half of 1 percent to the nation's pharmaceutical bill. Yet, while it is predicted that better drug treatment information will permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays, physician visits and parental workdays lost, the extended exclusivity will also delay the introduction of lower-priced generic drugs into the market. Delaying the introduction of generic drugs from entering the markets temporarily raises the average price of prescription drugs, thus, particularly affecting the elderly and the uninsured population.

Although the report recommends renewal of the pediatric exclusivity provision after its sunset in 2002, it also recommends modifications to increase the program's effectiveness. The primary modification is for Congress

to develop alternative incentives to address gaps in the current law regarding specific groups of children and classes of drugs for which current exclusivity provisions are inadequate or do not apply. Moreover, the status report acknowledges the great burden the provision places on the elderly and the uninsured because of the delay in generic drugs on the market as a result of the extension of brand name patents under the provision. As such, it encourages Congress to weigh costs of the provision and, if Congress determines that the costs of the provision outweighs its benefits, then the size of the incentive should be reduced.¹³⁶ When viewed in its totality, however, the report concludes that the pediatric exclusivity provision has been effective in achieving its goal of providing dosing and safety information to physicians and to consumers by having information regarding safety on product labels.¹³⁷

VII.

RECOMMENDATIONS FOR MODIFICATION TO THE PEDIATRIC EXCLUSIVITY PROVISION¹³⁸

The purported successes of the Modernization Act in encouraging drug sponsors to conduct more clinical trials including children with the opportunity for patent extension on the tested drug make it difficult to question whether Congress should renew the provision beyond its scheduled sunset date of January 1, 2002. There is more information regarding the effects of drugs on children available to clinicians for administering drugs to children and more information for product labeling than ever before.

In considering whether to renew the pediatric exclusivity provision, as suggested by the status report, Congress must seriously evaluate the costs of granting such an incentive and, more importantly, evaluate

¹³⁶See Status Report to Congress at 18.

¹³⁷See generally, Status Report to Congress, *supra* note 134.

who is actually bearing the burden of these costs. It is estimated that over the next 20 years, the pediatric exclusivity provision will cost consumers an additional 13.9 billion dollars. Over that time, according to the FDA's projections, brand-name drug-makers will gain 29.6 billion dollars, the generic industry will lose 10.7 billion dollars, and drug distributors, including pharmacies will lose 4.9 billion dollars.¹³⁹ Assuming this is an accurate estimate, an evaluation of these numbers reveals that the overwhelming financial burden of the pediatric market exclusivity provision lies with the consumer. The extension of market exclusivity to name brand drugs keeps the prices of prescription drugs higher due to the unavailability of generic drugs. More than likely, the most affected sector of the population is the elderly and the poor. To counter the effects of the provision's incentive on these populations, Congress should revise the Modernization Act and implement a two-tiered incentive plan for drug sponsors that conduct clinical trials inclusive of the pediatric population.

A two-tiered incentive plan would not only lessen the burden on consumers, particularly the elderly and the poor populations, but it would also combat the shortcomings of the Modernization Act including (1) its failure to encourage testing about the effects of drug therapy on all sectors of the pediatric populations, including neonates and infants; and (2) the absence of an incentive to conduct testing on drugs that do not qualify for patent exclusivity extensions due to expired patents. Moreover, a two-tiered incentive plan will further increase the amount of information available regarding the effects of commonly prescribed drugs on the pediatric population, which is the ultimate goal of the provision.

Tier-one of the incentive plan would allow the pediatric exclusivity provision to remain similar to its present state, with some modifications. As the provision stands today, a drug that has been tested on children

¹³⁹S. Stolberg, Children Test New Medicines Despite Doubts, N.Y. Times (February 11, 2001) at 1.

for safety and efficacy may qualify for a six-month extension on its patent, provided that the patent has not already expired. Congress should modify this and allow drugs to qualify for a **nine-month** extension under the pediatric exclusivity provision if (1) the tested drug leads to a change in labeling for the pediatric population; (2) the drug is the first in its particular therapeutic class to be tested on children; or (3) the drug has been tested on all cross-sections of the pediatric population, including neonates and infants.

Limiting the drugs that qualify for patent exclusivity achieves many of the goals the pediatric exclusivity provision fails to meet in its present state. Most significantly, such limitations will reduce the number of drugs that receive the market exclusivity incentive, thus, lessening the burden on consumers. While these requirements set the incentive qualifying bar for drug sponsors higher, the financial gain drug sponsors receive as a result of the new nine-month patent exclusivity would make it worth the extra effort. These limitations essentially shift the financial burden from consumers to drug sponsors, while simultaneously providing them a highly valuable and attainable incentive.

In addition to shifting the burden of the incentive plan from consumers to drug sponsors, these limitations will encourage faster and better pediatric studies, especially with the granting of market exclusivity to only the first drug of a particular therapeutic class. This provision is similar to the standard used in the orphan drug context, where a subsequent sponsor seeking orphan status must show clinical superiority in order to defeat a previous sponsor's orphan exclusivity for a particular drug and qualify for its own exclusivity. As a result of this modification, there will be fewer unnecessary duplicative studies on drugs of the same class. Furthermore, drug companies would not be able to maintain market exclusivity on an entire class of drugs that essentially provide the same treatments, thus, rarely providing any new information on the effects of these treatments on children.

The final provision under which a drug sponsor can get an extension on market exclusivity of a drug is by testing the drug on all cross-sections of the pediatric population. While there has been a substantial increase in the information available about the effects of certain drug therapies on certain pediatric populations as a result of the incentives provided in the Modernization Act, information regarding the effects of drug therapies on infants and neonates is still insufficient. As such, this provision for patent exclusivity extension will encourage drug sponsors to conduct clinical trials in this sector of the pediatric population as well.

Although limiting grants of patent exclusivity to those drugs that meet the previously outlined criteria, Congress should also create a second-tier incentive to ensure that drug companies do not dismiss the Modernization Act incentive provision as unattainable, and forego all pediatric clinical trials. There should be an alternative, second-tier incentive for drug sponsors to test drugs in pediatric populations that will not qualify for the market exclusivity extension, such as those drugs with expired patents, drugs of a class that have already received the extension under the first-tier, and drugs for which it is too costly or unfeasible to design a plan for testing on neonates and infants. This second-tier incentive would be to provide drug companies with a one time tax benefit to conduct such studies. This benefit rewards drug companies without burdening consumers and drug distributors through excessive grants of market exclusivity, which delay the entrance of generic drugs and other lower price competitors into the market. Although this provision may not be as appealing as the extension on market exclusivity as provided in the first-tier, it will encourage drug sponsors to conduct testing of their drugs on children, especially if the tax incentive is substantial.

Under this proposed scheme, the Modernization Act will continue to increase the amount of information available to clinicians and for labels regarding the effects of drug therapies on children by offering drug sponsors incentives to conduct such testing. Placing further limitations on drugs that qualify for patent

exclusivity will alleviate the economic burden consumers, especially the most vulnerable of our population, experience as a result of the delay of the introduction of lower drug competitors into the market. While extension of market exclusivity from six- months to nine-months for qualifying drugs may have a counter effect and further delay the entry of some generic drugs into the market, the strict limitations of this provision will keep such to a minimum. Finally, the second-tier incentive, which will provide a one time tax benefit for drugs that have been tested on children but do not qualify under the first-tier, will encourage drug sponsors to conduct clinical trials in the pediatric population, especially testing drugs on children that already have expired patents, without causing economic harm to consumers and drug distributors.

CONCLUSION

More than 60 to 70 percent of all drugs have no indication for their use in children under age 12. The Final Rule and the pediatric exclusivity provision are the latest efforts to solve this problem of children as “therapeutic orphans.” Although the FDA Final Rule mandates drug sponsors to conduct clinical trials that include children, the statutory authority of the FDA to enforce such a rule is questionable, and may be challenged by the pharmaceutical industry in the future. As such, it is imperative that Congress renew the pediatric exclusivity provision in the FDAMA so as to continue increasing the amount of information available about the effects of drugs in children. In renewing this provision, Congress should adopt an incentive plan that rewards drug manufacturers for conducting such clinical trials but not one that simultaneously harms consumers. Thus, a two-tiered incentive plan which extends patent life to drug studies providing the most comprehensive information about their effects in children and tax benefits to other drug studies that include children, is an alternative, and perhaps better plan, for the pediatric exclusivity provision of the Modernization Act.